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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 4 : G01N 21/65, A61B 5/00 — A1

(11) International Publication Number: WO 88/ 06726

(43) International Publication Date: 7 September 1988 (07.09.88)

(21) International Application Number: PCT/GB88/00125

(22) International Filing Date: 24 February 1988 (24.02.88)

(31) Priority Application Numbers: 8704423, 8722449

(32) Priority Dates: 25 February 1987 (25.02.87), 24 September 1987 (24.09.87)

(33) Priority Country: GB

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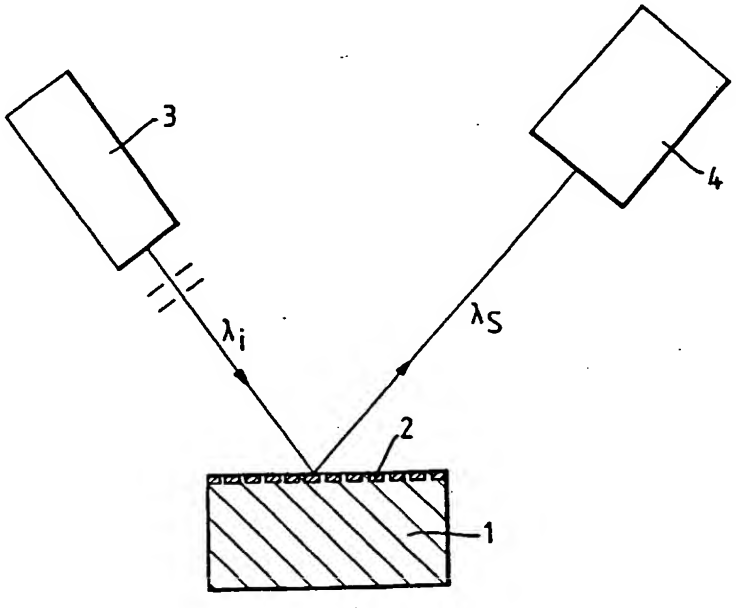
(81) Designated States: AT (European patent), AU, BE (European patent), CH (European patent), DE (European patent), FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent), US.

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: IN VIVO BLOOD TESTING



(57) Abstract

Apparatus is disclosed for sensing blood gas concentration *in vivo*, which comprises a probe adapted for emplacement in a vein or artery and including: (a) at one end thereof, a gas-permeable membrane formed of a biologically acceptable material; (b) contiguous with said membrane, an active surface in the form of a surface capable of supporting a plasmon resonance; and (c) a light guide of a type capable of transmitting a light input to said active surface and of transmitting a light output away from said active surface, without mutual interference, wherein the light guide constitutes a support or substrate for said active surface and is in optical communication therewith.

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IN VIVO BLOOD TESTING

This invention relates to in vivo blood gas analysis using Raman spectroscopy.

Vibrational spectroscopy has been employed for many years to study the structure and bonding of molecules. As each bond has its own, characteristic frequency, vibrational spectra and molecular structure are related. In this way, compositional analysis can be carried out by inspecting the vibrational spectrum of a sample and comparing it with the spectra of known compounds.

The two main techniques employed are infrared absorption and Raman spectroscopy. In the first case, a wavelength tunable or broadband light source is used to illuminate the specimen, and the wavelengths at which energy is absorbed are recorded. In Raman spectroscopy, a fixed wavelength source is employed, and the spectrum of emitted radiation recorded; the maxima in the emission spectrum represent the difference in energy between the incoming light quanta and the vibrational energy of the molecular bonds in the sample.

In general, vibrational energy levels lie in the infrared, and this represents a disadvantage for infrared absorption spectroscopy. Ideally one requires a tunable or broadband source of IR radiation. Although this is clearly possible using thermal radiation, in general power levels are low, and detectors with the required sensitivity are expensive.

With Raman spectroscopy, however, one can illuminate the sample in the visible waveband, for example using a fixed frequency laser, and generate an emitted spectrum, shifted to the red, representative of the sample composition.

The major disadvantage to Raman scattering is that it is a weak process, relying on a non-linear interaction between the source radiation and the sample. In the past this has meant that even for concentrated samples under

ideal conditions photon counting and photomultiplier tubes have to be employed to detect the emitted radiation. Remote detection, when the sample volume may be small, or dilute, has therefore been impractical.

In the technique we propose, a method of compositional analysis utilises the enhancement of the efficiency of generation of the Raman spectrum by using a configuration in which a surface plasmon is excited in an appropriate surface layer and the Raman spectrum is simultaneously generated. It is known that when a surface plasmon is excited, the electric field associated with the electromagnetic wave is highly enhanced (by a factor of 10^3 to 10^4). This means that it will interact with high efficiency with molecules in close proximity to the surface; the excitation efficiency of the Raman spectrum is much higher than would be the case without the surface plasmon phenomenon. In addition, excited molecules in close proximity to a metal surface can radiate light by co-operating with the metal surface; the 'image' of the molecular dipoles acts with the molecules themselves to form a 'phased array' of emitters. This emission can interact with the surface plasmon resonances of the metal surface so that the light is emitted in known, calculable directions. Thus the collection efficiency of the Raman spectrum is enhanced.

The present invention is particularly concerned with a sensor head designed specifically for use in <u>in vivo</u> monitoring of blood gases. The sensor is capable of both identification of gases and continuous measurement of their concentration.

In blood gas analysis, one is usually concerned with the measurement of O_2 and CO_2 partial pressures in both arterial and veinous flow, although the technique of the present invention may also be applicable to the detection of other analytes. Current techniques are based on either electrochemical (potentiometric or amperometric) or optical sensors. For example, the

Cardiomet 4000 system manufactured by Biomedical Sensors Limited of High Wycombe, UK combines pO_2 measurement using an electrochemical sensor based on a Clark electrode with pCO_2 and pH measurement based on the optical absorption properties of chemical dyes. Electrochemical sensors suffer from some problems associated with their complexity and fragility which makes for example miniaturisation of the sensors difficult. This is particularly relevant to <u>in vivo</u> blood gas analysis.

There have been recent developments in electrochemical sensors, such as the use of ion selective field effect transistors (ISFETS). However the productionisation of such systems has not yet been fully addressed.

In addition to optical sensors based on absorption and fluorescence, fibre optic sensors, either extrinsic or intrinsic, can be developed for application in blood gas analysis. The problem with such intrinsic sensors is the identification of a transduction mechanism appropriate to the particular parameter which is to be sensed.

The present invention utilises a single optical technique for the monitoring of a number of blood gases e.g. pO_2 and pCO_2. The technique is also applicable to the detection and measurement of other blood gas analytes. Its simplicity compared with electrochemical sensors and versatility to monitor a plurality of analytes make it an attractive alternative sensor technology.

The present invention provides a method of analysis which utilises enhancement of the efficiency of Raman spectrum generation in a configuration in which a surface plasmon resonance is generated in an appropriate surface layer and the Raman spectrum is generated (normally simultaneously with the plasmon excitation).

According to one aspect of the present invention, there is provided apparatus for sensing blood gas concentration in vivo, which comprises a probe adapted for emplacement in a vein or artery and including: (a) at one end thereof, a gas-permeable membrane formed of a biologically acceptable material; (b) contiguous with said membrane, an active surface in the form of a surface capable of supporting a plasmon resonance; and (c) a light guide of a type capable of transmitting a light input to said active surface and of transmitting a light output away from said active surface, without mutual interference, wherein the light guide constitutes a support or substrate for said active surface and is in optical communication therewith.

Conveniently, the light guide comprises a pair of parallel optical fibres, one acting as an afferent light guide and the other as an efferent light guide.

In practice, the gas-permeable membrane will come into contact with a patient's blood and dissolved gases (O_2 and CO_2) will cross the membrane and contact the active surface. This is then illuminated by radiation arriving via the afferent fibre and a plasmon resonance-enhanced Raman spectrum is collected by the efferent fibre and directed towards a remotely located spectral detection system.

The active surface can be in the form of a metal-coated grating or prism surface. Alternatively the surface may be constituted by a dispersion of small metal spheres, as will be described in more detail hereinafter.

The invention will now be described in more detail by way of example, with reference to the accompanying drawings, in which:

FIGURE 1 is a schematic illustration of the generation of a surface plasmon resonance enhanced Raman spectrum;

FIGURES 2a and 2b illustrate schematically two embodiments ot the active surface used in the invention;

FIGURE 2c illustrates schematically the production of a Raman spectrum;

FIGURES 3 and 4 are schematic illustrations of two arrangements in accordance with the invention;

FIGURE 5 illustrates an alternative embodiment of the active surface; and

FIGURES 6 to 9 illustrate four arrangements of a probe in accordance with the inventions each incorporating a different active surface/light collecting arrangement.

Referring now to the drawings, the general layout is as shown in Figure 1. It will be appreciated that components shown in the drawings are not drawn to scale; the enlargement of certain items whose dimensions are of the order of the wavelength of light is necessary for clarity. A sensor head 1 supports an active surface 2 which, in this embodiment, is in the form of a grating. A source 3 of coherent radiation, e.g. a laser operating in the visible or near infra-red, produces a collimated beam $lambda_i$ which is directed at the active surface 2 at an angle of incidence $theta_i$. Surface plasmon enhanced Raman emission occurs and the emitted rays $lambda_S$ are detected by a detection system 4. The illumination source and detection systems do not form a part of the present invention. In the presence of a material, e.g. a specific gas, whose presence is to be detected, the enhanced Raman emission is affected in a specific and detectable manner; in this way, the detection and measurement of the Raman emission is used to give a qualitative and/or quantitative indication of the presence of the material.

The sensor itself comprises a metal coated substrate which may be part either of a prism (also known as Kretchmann or Otto geometry) or of a grating assembly. These arrangements are shown schematically in Figure 2. As shown in Figure 2c, the metal grating has a dielectric constant E_M while the dielectric medium onto which the

metal layer is deposited has a dielectric constant E_i. Surface plasmon generation can occur at the metal dielectric interface E_i, E_m. The wavelength and angle of incidence of the illumination source, and the pitch, depth and groove shape of the grating (if used) are chosen to ensure efficient surface plasmon generation at the interface. This configuration, in which surface plasmon and Raman spectrum are generated simultaneously, provides enhancement of the efficiency of Raman spectrum generation.

In Figure 2a, the sensor head comprises a prism which carries a metal film 2 on one surface; the film 2 communicates directly with a conduit C through which the material undergoing analysis is passed. The arrangement of Figure 2b is different in that the active metal film 2 is spaced from the prism by a narrow gap (e.g. of 1 micrometre or less) which forms part of the conduit C.

It is a feature of the in vivo blood gas sensor to which this invention relates that the sensor head is positioned remote from the illumination source, for example at the end of a catheter assembly which can be inserted into the patient's blood flow in a vein or artery. The illuminating light is transmitted to the sensor, e.g. via an optical fibre, with the generated Raman spectrum returning to the main instrument via the same route. A single fibre or two fibres, delivery and receiver, may be used. This is shown in diagrammatic form in Figures 3 and 4. In Fig. 3, there is a single optical fibre 5 which conveys light at 6 from the illumination system (not shown) to the sensor assembly 1 and also conveys the Raman emission at 7 from the sensor assembly 1 to the detector system (not shown). In Fig. 4, two separate optical fibres are located in a conduit 8 and serve to transmit the afferent illumination 6 and the efferent signal 7.

Particular features of the in vivo sensor head are described below. Highly efficient surface plasmon

generation can occur at a metal-dielectric interface when the momentum of the incident radiation and the surface plasmon are matched. This does not occur under normal circumstances, since the surface plasmon momentum is always less than that of light. However momentum matching can be achieved by a number of techniques:

i) Metal coated Prism ATR (attenuated total internal reflection), also known as Otto or Kretchmann geometry configuration as shown in Figures 2a and 2b. At a particular angle of incidence, the momentum of the evanescent wave matches the surface plasmon mode ensuring efficient surface plasmon generation.

ii) Use of a metal coated grating to ensure momentum matching (Figure 2c). The wavelength and angle of incidence of the illumination source and the grating pitch, depth and groove shape are chosen to ensure efficient surface plasmon generation at the interface. Illumination from the dielectric side of the grating is possible if the metal coating is sufficiently thin ($< 10'_s$ nm) to allow penetration of the enhanced electric field into the material to be sensed.

iii) It is known that under optimised conditions of physical parameters efficient surface plasmon generation can occur when a colloidal suspension of metalised spheres is illuminated. The dimensions of the spheres should be comparable with the wavelength of light. Figure 5 illustrates this arrangement, where the metal coated spheres 9 are located in a housing which constitutes the sensor head 1.

iv) Surface plasmon generation can also occur at a statistically rough metal-dielectric interface.

We now describe ways in which some of these geometries could be integrated with a catheter based delivery system for in vivo blood gas analysis.

Unique features of this sensor are as follows.

A sub-miniature system allowing delivery of the complete sensor into the blood supply, remote from the illumination source and detection systems.

Intregration of the light delivery and collection systems (fibres) and the interaction surface. For example:

i) As shown in Fig. 6, the end of the fibre 5 may be metal coated as at 11. Dielectric cladding 10 surrounds the fibre 5. A gas-permeable membrane 12 overlies the metal layer 11. Surface plasmon generation can then occur in a similar way to the Kretchmann geometry of Figure 2a. Here "free space" propagation of the conventional Kretchmann arrangement is replaced by a coupling of a propagation mode of the fibre to the surface plasmon mode. Raman scattered light can be collected by the same fibre.

ii) Minaturised and integrated fibre grating assemblies are shown in Figure 7. A spherical collimating lens 13 is attached to the end of the fibre 5 which provides illumination and a combined membrane/grating support 14 is provided between the lens 13 and a grating 15. Alternatively, a fibre structure could be moulded into the fibre tip and metallised, as at 15 in Figure 8.

iii) An arrangement utilising a colloidal suspension of metal spheres is shown in Figure 9.

In all the described configurations, it is essential that the sensor areas be surrounded by a membrane structure (indicated as either 12 or 14) permitting the flow of blood gases into the sensor volume but preventing the sensor from coming into direct contact with the blood. The total diameter of the sensor should not exceed 2 mm.

Claims:

1. Apparatus for sensing blood gas concentration in vivo, which comprises a probe adapted for emplacement in a vein or artery and including: (a) at one end thereof, a gas-permeable membrane formed of a biologically acceptable material; (b) contiguous with said membrane, an active surface in the form of a surface capable of supporting a plasmon resonance; and (c) a light guide of a type capable of transmitting a light input to said active surface and of transmitting a light output away from said active surface, without mutual interference, wherein the light guide constitutes a support or substrate for said active surface and is in optical communication therewith.

2. Apparatus as claimed in claim 1, wherein said light guide comprises a pair of optical fibres, one functioning as an afferent light guide and the other functioning as an efferent light guide.

3. Apparatus as claimed in claim 1 or 2, wherein said surface is a grating.

4. Apparatus as claimed in claim 1 or 2, wherein said surface is a metal coated fibre.

5. Apparatus as claimed in claim 1 or 2, wherein said surface is a suspension of metal particles whose dimensions are of the order of the wavelength of light.

6. Apparatus as claimed in claim 1 or 2, wherein said surface is a statistically rough surface.

7. Apparatus as claimed in claim 1 or 2, wherein said surface is a prism one surface of which is coated with a thin film of a metal.

8. Apparatus as claimed in any preceding claim, wherein said active surface, said gas-permeable membrane and said light guide are housed in a catheter.

9. Apparatus as claimed in claim 8, which further comprises a source of coherent light located remote from said active surface but optically in communication therewith via said light guide.

Fig. 1.

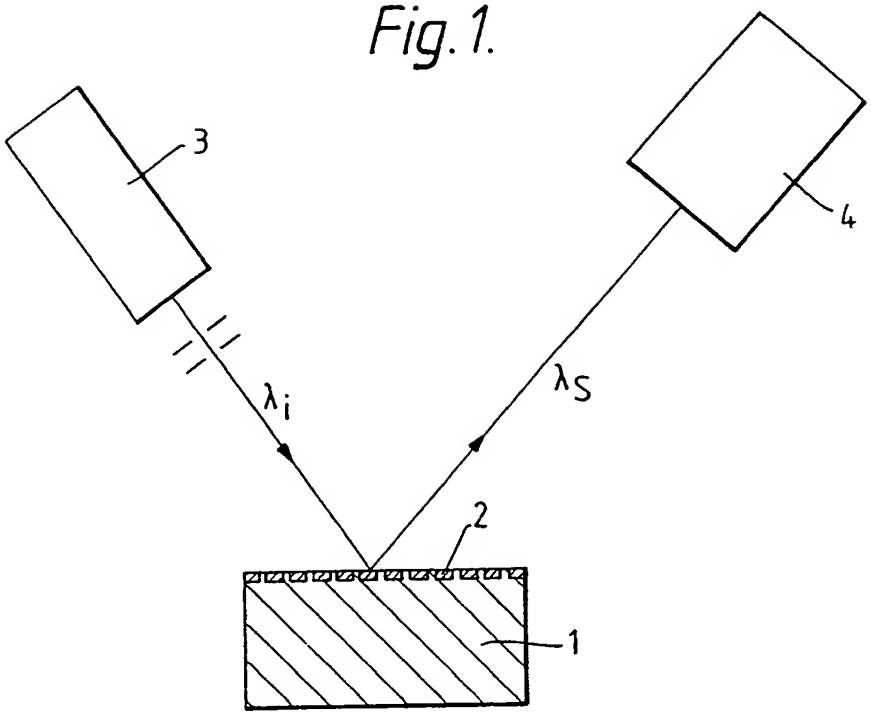


Fig. 2a.

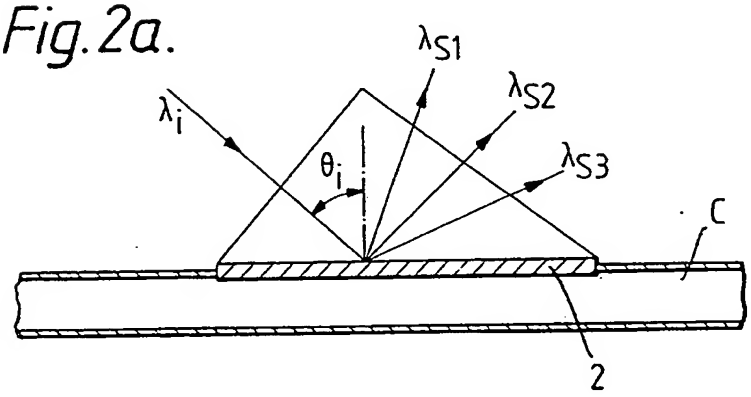


Fig. 2b.

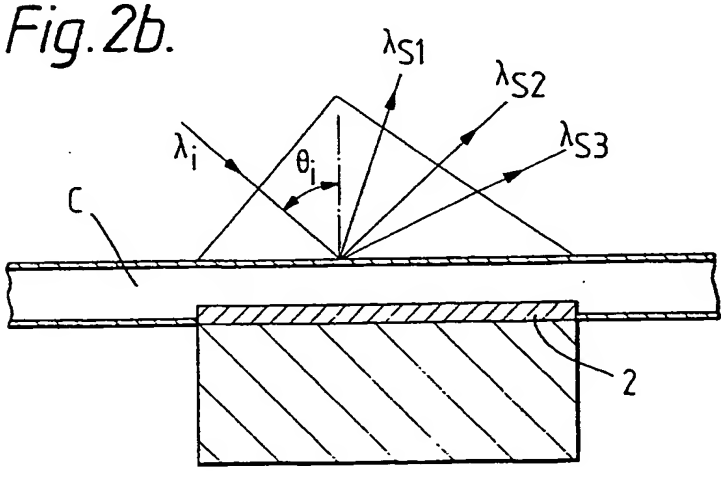


Fig.2c.

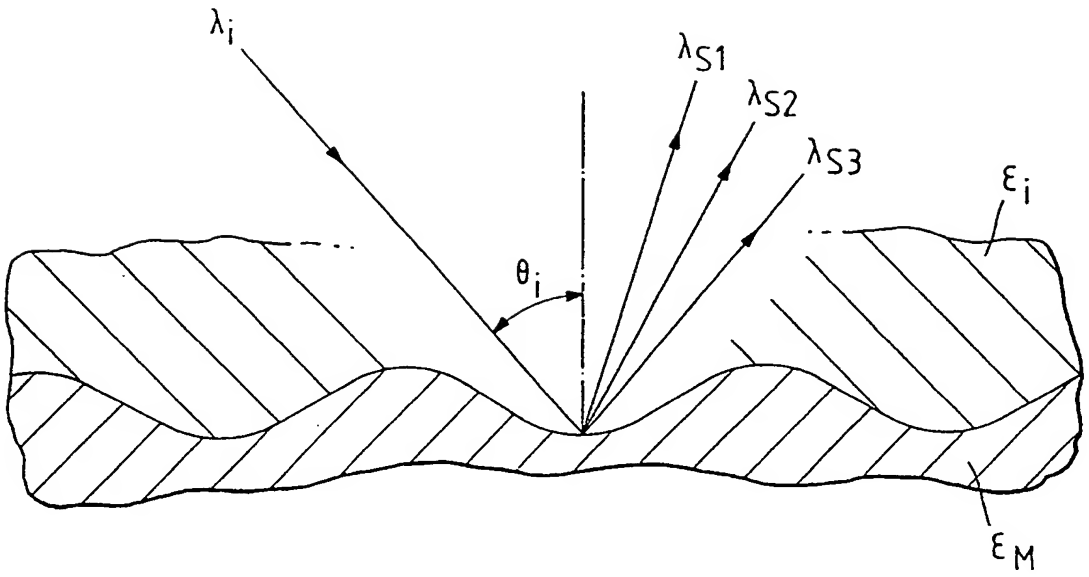


Fig.3.

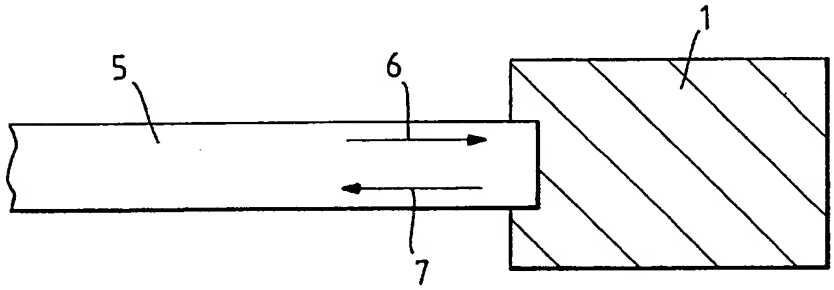


Fig.4.

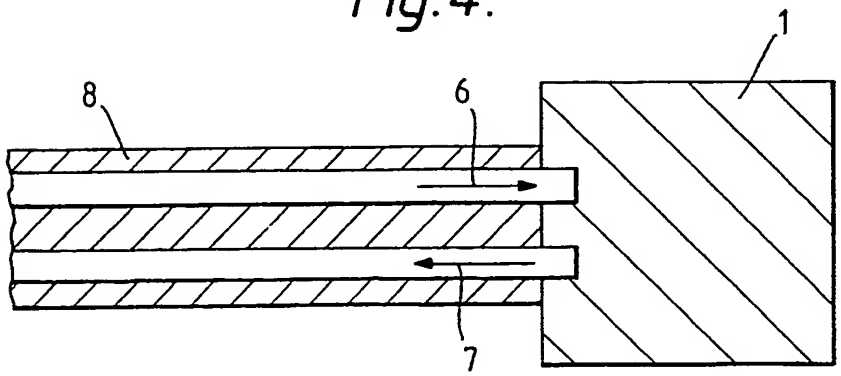


Fig.5.

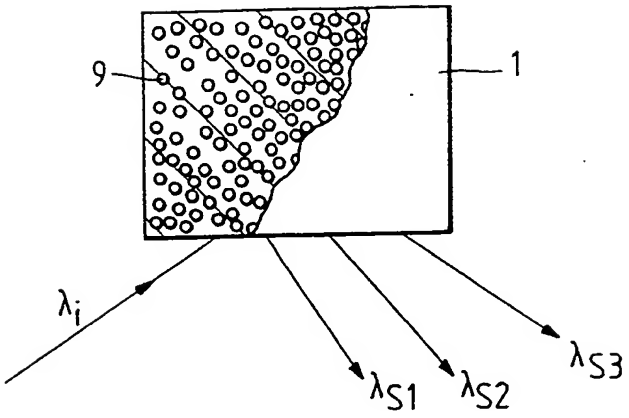


Fig.6.

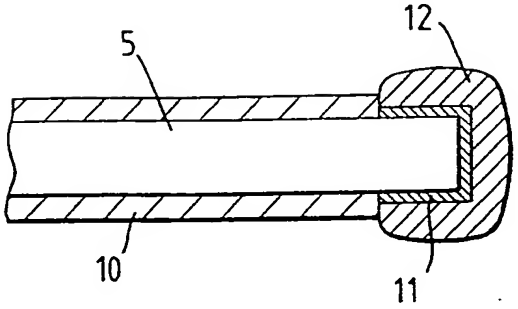


Fig.7.

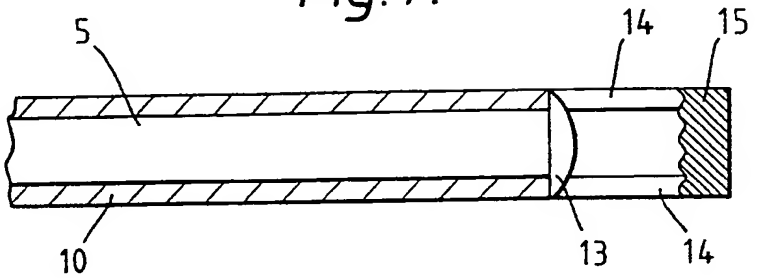


Fig.8.

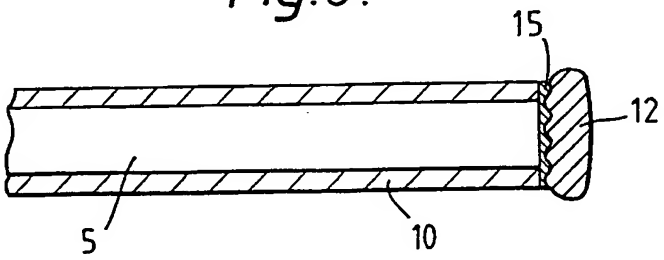
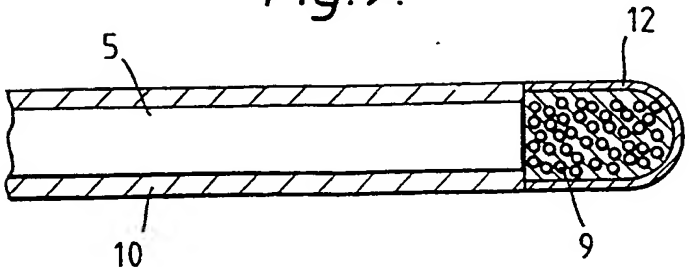


Fig.9.



INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 88/00125

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: G 01 N 21/65; A 61 B 5/00

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	A 61 B 5/00; G 01 N 21/55; G 01 N 21/17; G 01 N 21/77; G 01 N 21/65

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	Analytical Chemistry, volume 54, no. 9, August 1982, American Chemical Society, (US), I. Chabay: "Optical waveguides", pages 1071 A - 1080 A see page 1074 A, left-hand column, "This protruding field", middle and right-hand column; page 1077 A, paragraphs 1,2 --	1,2,7
A	IBM Technical Disclosure Bulletin, volume 23, no. 11, April 1981, (New York, US), J.G. Gordon et al.: "Use of gratings to detect small quantities of materials by raman spectroscopy", page 5099 see the whole article --	1,3
A	GB, A, 2173895 (PLESSEY CO.) 22 October 1986 see page 1, lines 44-61 --	3,5,7
A	IEEE Transactions on Biomedical Engineering, volume BME-33, no. 2, February 1986, IEEE, (New York, US),	1,2,8,9

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* Special categories of cited documents: [10]

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
2nd June 1988	5 JUL 1988
International Searching Authority: EUROPEAN PATENT OFFICE	Signature of Authorized Officer: P.C.G. VAN DER PUTTEN

Form PCT/ISA/210 (second sheet) (January 1985)

International Application No. PCT/GB 88/00125

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
	J.L. Gehrich et al.: "Optical fluorescence and its application to an intravascular blood gas monitoring system", pages 117-132 see pages 118-120, "Blood gas probe design"; pages 121-122, "Optical pO_2 sensor" and "Instrument design"	

See notes on accompanying sheet

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 8800125 SA 20932

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 20/06/88
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A- 2173895	22-10-86	EP-A- 0202021	20-11-86
		JP-A- 61292045	22-12-86